Topics in Primary Care Medicine

Prophylaxis Against Opportunistic Infections in Patients Infected With the Human Immunodeficiency Virus

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The prevention of opportunistic infections has become one of the most important components in the care of patients infected with the human immunodeficiency virus (HIV). The progression of HIV infection to advanced cellular immune incompetence predictably increases the risk of specific opportunistic infections. As host defenses wane, the likelihood of infections rises, first with more virulent pathogens such as *Streptococcus pneumoniae* and *Mycobacterium tuberculosis*, then with the true opportunists such as *Pneumocystis carinii* and cytomegalovirus (CMV). The probability of an infection occurring depends on the interplay of host immunity, pathogen prevalence and virulence, and the use of prophylaxis. The efficacy of prophylaxis for *P carinii* pneumonia was demonstrated early in the acquired immunodeficiency syndrome (AIDS) epidemic, and it has since been found to improve survival and slow the progression of HIV disease.[1-3] This success of *P carinii* pneumonia prevention has encouraged research on prophylaxis against other opportunistic infections. The introduction of new preventive therapies to the standard care of patients with HIV depends on their efficacy, tolerability, convenience, cost, and effects on quality of life. Detailed recommendations for preventing opportunistic infections were recently published by the United States Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA).[4] In this review, we will consider current strategies for the prevention of opportunistic infections in adult patients with HIV infection. Preventing opportunistic infections in children with HIV infection is considered elsewhere.[4]

Pneumocystis carinii Pneumonia

Pneumocystis carinii pneumonia is the most common serious opportunistic infection among patients with AIDS in the United States. This pneumonia will develop eventually in at least 75% of HIV-infected patients in the absence of prophylaxis. The risk of infection increases with decreasing CD4 counts. The Multicenter AIDS Cohort study found that HIV-infected patients with CD4 counts of 201 to 350 $\times$ 10^6 per liter (201 to 350 per mm^3) had a 4.0% incidence of *P carinii* pneumonia within a year, whereas the incidence was 44.4% among those with CD4 counts of less than 100 $\times$ 10^6 per liter.[5,6] Patients with a history of *P carinii* pneumonia have a recurrence rate of 70% within a year in the absence of prophylaxis.[7] Because *P carinii* pneumonia is so common and because the mortality rate is 15% to 20% per episode,[8] prophylaxis is imperative for patients at risk for the disease. The USPHS-IDSA guidelines recommend prophylaxis for patients with a history of *P carinii* pneumonia; those with CD4 counts of less than 200 $\times$ 10^6 per liter; and patients with unexplained temperatures of greater than 37.8°C (100°F) for more than two weeks or oropharyngeal candidiasis, which have been associated with an increased risk of *P carinii* pneumonia irrespective of the CD4 count.[9] Three prophylactic regimens are currently widely used: the combination drug of trimethoprim and sulfamethoxazole, dapsone, and aerosolized pentamidine isethionate.

Trimethoprim and Sulfamethoxazole

The combination of trimethoprim and sulfamethoxazole is more than 95% effective in preventing *P carinii* pneumonia when patients adhere to therapy.[10] Several comparative trials have shown the use of trimethoprim-sulfamethoxazole to be superior to that of aerosolized pentamidine for primary and secondary prophylaxis. In a randomized primary prophylaxis trial with an average follow-up of 8.8 months, none of 142 patients assigned to receive trimethoprim-sulfamethoxazole (either 1 single-strength or 1 double-strength tablet daily) had *P carinii* pneumonia develop compared with 6 of 71 (8.4%) patients assigned to receive aerosolized pentamidine isethionate (300 mg monthly).[11] In a randomized trial of secondary prophylaxis, the recurrence rate for *P carinii* pneumonia was 3.5% per year in patients receiving

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
HIV = human immunodeficiency virus
IDSA = Infectious Diseases Society of America
Ig = immunoglobulin
USPHS = United States Public Health Service

trimethoprim-sulfamethoxazole, one double-strength tablet daily, compared with 18.5% in patients receiving aerosolized pentamidine, 300 mg monthly.[12]

Trimethoprim-sulfamethoxazole also appears to be more effective than dapsone for primary prophylaxis. The AIDS Clinical Trials Group study 081 observed 842 patients an average of 39 months after randomization to receive either trimethoprim-sulfamethoxazole, one double-strength tablet twice a day; dapsone, 50 mg twice a day; or aerosolized pentamidine, 300 mg monthly.[10] In an intention-to-treat analysis, the number of episodes of *P carinii* pneumonia was about equal in each of the three groups. An analysis of assigned treatments at the time of *P carinii* pneumonia diagnosis, however, revealed that the use of trimethoprim-sulfamethoxazole was the most effective treatment. In those patients continuing their assigned regimen, *P carinii* pneumonia occurred at a rate of 1.2 episodes per person-year among patients taking trimethoprim-sulfamethoxazole, 2.6 episodes per person-year for patients taking dapsone, and 5.7 episodes per person-year for patients taking aerosolized pentamidine. In a study of intermittent therapy, the cumulative two-year incidence of *P carinii* pneumonia was 11% among patients assigned to receive dapsone, 100 mg, plus pyrimethamine, 50 mg, twice a week compared with 0% among patients assigned to take trimethoprim-sulfamethoxazole, one double-strength tablet twice per day three times a week.[13]

Side effects are common among patients taking trimethoprim-sulfamethoxazole and are often severe enough to require discontinuation of the drug. The most common of these are fever, rash, leukopenia, and nausea. In the AIDS Clinical Trials Group study 081, 51% of the patients receiving trimethoprim-sulfamethoxazole discontinued their treatment because of adverse effects.[10] The dose used in the study was two to four times the doses used in current practice, however, and adverse reactions to trimethoprim-sulfamethoxazole appear to be dose-dependent.[11] Oral desensitization to trimethoprim-sulfamethoxazole in patients with previous adverse reactions has been advocated by some clinicians.[14,15] The major toxic effects of trimethoprim-sulfamethoxazole are not mediated by immunoglobulin (Ig) E, however; thus, successful desensitization may merely reflect successful rechallenge with the agent because rechallenge at standard doses is tolerated by about half of patients with a history of mild drug reactions.[16] Comparative trials of rechallenge at full prophylactic dosages versus gradual dose escalation are needed to clarify this issue.

Trimethoprim-sulfamethoxazole is the preferred drug for *P carinii* prophylaxis. In addition to being the most effective agent, it appears to also protect against other opportunistic infections such as toxoplasmosis and infections with pyogenic bacteria.[12,17] The recommended dose is one double-strength tablet a day. Other regimens that appear to be effective include one single-strength tablet a day or one double-strength tablet three times a week.

Dapsone

Dapsone is now the second-line agent for *P carinii* pneumonia prophylaxis, with efficacy equal to or greater than aerosolized pentamidine.[10,18] As with trimethoprim-sulfamethoxazole, side effects are common, with about 42% of patients discontinuing dapsone because of adverse drug reactions.[10] These include rash, nausea, methemoglobinemia, and dose-related anemia. Severe hemolytic anemia may develop in patients with glucose-6-phosphate dehydrogenase deficiency, a condition that affects 11% of African Americans.[19] Patients of African-American and Mediterranean descent should have their glucose-6-phosphate dehydrogenase level checked before dapsone therapy is initiated. About 70% of patients who are intolerant to trimethoprim-sulfamethoxazole will tolerate dapsone.[20]

The minimal effective dose of dapsone for prophylaxis is not known. The USPHS-IDSA guidelines recommend using dapsone, 100 mg a day, the best-studied dose.[4] The use of dapsone, 100 mg per week, in combination with pyrimethamine was less effective than trimethoprim-sulfamethoxazole in preventing *P carinii* pneumonia,[13] and 50 mg a day was shown to be inferior to 100 mg a day.[10,18] As with trimethoprim-sulfamethoxazole, patients who are intolerant of higher doses of dapsone may tolerate lower doses.

Aerosolized Pentamidine Isethionate

Aerosolized pentamidine is the best alternative for patients intolerant of both trimethoprim-sulfamethoxazole and dapsone. The recommended regimen is 300 mg given monthly by the Respirgard II jet nebulizer. Because inhalation results in minimal systemic absorption, aerosolized pentamidine is well tolerated, with only 3% of patients discontinuing treatment because of adverse reactions.[11] The most common adverse reaction is cough and bronchospasm, especially in patients with a history of asthma. For such patients, pretreatment with an inhaled bronchodilator can improve tolerability.

In addition to lower prophylactic efficacy, there are several other drawbacks to the use of aerosolized pentamidine. It has been associated with atypical presentations of *P carinii* infection, including upper lobe infiltrates and extrapulmonary disease,[21,22] as well as pneumothorax.[23,24] Because of the potential for facilitating tuberculosis transmission, the Centers for Disease Control and Prevention recommends that aerosolized pentamidine be administered in areas with negative pressure ventilation and that patients be assessed for symptoms of tuberculosis at each visit.[25] Finally, the cost of pentamidine is $1,200 per year, not including the cost of administration, whereas trimethoprim-sulfamethoxazole and dapsone cost less than $50 per year.[26]

Other Regimens

Administering pentamidine intravenously, 4 mg per kg a month, was found to be effective in preventing *P carinii* pneumonia in a case series of 52 patients.[27] There was one case of pneumocystosis in 587 patient-months of prophylaxis. Likewise, in a case series of 96 patients receiving intramuscular pentamidine (4 mg per kg up to 300 mg a month), there were only 3 cases of *P carinii* pneumonia in 776 months of patient follow-up.[28] In both studies, however, patients had adverse reactions commonly associated with the use of parenteral pentamidine, including hypotension and hypoglycemia. Given the substantial adverse reactions and lack of controlled trials, the use of parenteral pentamidine is not currently recommended for *P carinii* prophylaxis.

Atovaquone, clindamycin and primaquine phosphate in combination, trimethoprim and dapsone in combination, and pyrimethamine and sulfadiazine in combination have been used as prophylactic regimens but are not recommended for routine use until further data are available. The suspension of atovaquone has substantially better bioavailability than the previously available tablet formulation and is being studied for use as a prophylactic agent.

Toxoplasmosis

Toxoplasmic encephalitis in patients with AIDS is usually a result of the reactivation of latent infection. Thus, patients who are seronegative for anti-*Toxoplasma* IgG are at low risk for disease.[29] In the United States, anti-*Toxoplasma* seropositivity ranges from 10% to 40%, and encephalitis will eventually develop in a third of IgG-positive HIV-infected patients.[30] Prophylaxis is therefore targeted at patients who are seropositive for anti-*Toxoplasma* IgG and are sufficiently immunosuppressed for toxoplasmic encephalitis to develop, usually when the CD4 counts are less than 100×10^6 per liter.

Trimethoprim-sulfamethoxazole appears to be the most effective drug in preventing the reactivation of toxoplasmosis. In a retrospective study of patients on *P carinii* pneumonia prophylaxis, toxoplasmosis did not develop in any of the 60 patients taking trimethoprim-sulfamethoxazole (1 double-strength tablet twice a day, 2 days per week) compared with 12 of 95 (13%) taking pentamidine ($P = .014$).[31] Toxoplasmosis developed in 33% of patients on pentamidine therapy who were seropositive for *Toxoplasma gondii*. Similarly, in a prospective study of *P carinii* pneumonia prophylaxis comparing the use of trimethoprim-sulfamethoxazole with that of pentamidine, only 1 of 10 cases of toxoplasmosis occurred in patients receiving trimethoprim-sulfamethoxazole.[12] In a European trial of antiretroviral therapy in which 73% of patients were seropositive for *T gondii*, toxoplasmic encephalitis developed in only 1 of 80 (1.3%) patients taking trimethoprim-sulfamethoxazole, compared with 30 of 228 (13.2%) taking aerosolized pentamidine ($P = .002$).[32]

Dapsone with pyrimethamine also appears to be effective in preventing toxoplasmosis. In a randomized study of trimethoprim-sulfamethoxazole (2 double-strength tablets 3 times a week) compared with dapsone (100 mg a week) plus pyrimethamine (25 mg a week), toxoplasmosis occurred in 2 of 81 (2.5%) patients on trimethoprim-sulfamethoxazole therapy compared with 3 of 85 (3.5%) patients on a regimen of dapsone and pyrimethamine.[33] In another prophylaxis trial in an area highly endemic for toxoplasmosis, the disease developed in 5 of 173 (2.9%) patients receiving dapsone (50 mg a day) and pyrimethamine (50 mg a week) compared with 28 of 176 (15.9%) patients receiving aerosolized pentamidine.[34]

Of other agents studied for prophylaxis, pyrimethamine alone was ineffective,[35,36] and its use was associated with increased mortality in one study.[37] Clindamycin prophylaxis produced unacceptably high rates of diarrhea and rash.[38] Other regimens requiring further study include atovaquone, dapsone as a single agent, azithromycin, and clarithromycin. Patients who have had active toxoplasmic encephalitis require lifelong suppression.[30]

The USPHS-IDSA guidelines recommend that patients with anti-*Toxoplasma* IgG antibodies and CD4 counts of less than 100×10^6 per liter receive trimethoprim-sulfamethoxazole, one double-strength tablet daily.[4] Patients who cannot tolerate this regimen should receive dapsone, 50 mg a day, and pyrimethamine, 50 mg a week, with leucovorin calcium, 25 mg a week, to decrease hematologic toxicity. It is not known whether lower doses of leucovorin would be as effective in preventing pyrimethamine toxicity. Patients seronegative for anti-*Toxoplasma* IgG antibodies should avoid eating undercooked meat and should take precautions when handling cat feces to prevent infection with *T gondii*.

Mycobacterium tuberculosis Infection

Persons infected with HIV are at increased risk for active tuberculosis developing. These patients have a 2% to 10% yearly risk of the reactivation of latent infection.[39] Patients infected with HIV are also at increased risk for active disease as a result of primary infection.[40] Prophylaxis with isoniazid has been shown to decrease the incidence of active tuberculosis and improve survival in HIV-infected patients in areas endemic for tuberculosis.[41] In a randomized trial in Haiti, patients assigned to receive isoniazid, 300 mg a day, and pyridoxine, 50 mg a day, for 12 months had an 80% reduction in the incidence of tuberculosis and increased survival compared with controls assigned to receive vitamin B_6 only.[41] Taking isoniazid daily for six months resulted in a 60% decrease in the prevalence of active tuberculosis in a similar study in Zambia.[42]

Isoniazid prophylaxis is recommended for any HIV-infected person who meets one of the following criteria: a positive purified-protein derivative skin test (≥5 mm of induration), a history of a positive skin test without previous prophylaxis, or recent close contact with a person with active tuberculosis. The USPHS-IDSA guidelines recommend the use of isoniazid, 300 mg a day, for 12 months, supplemented with pyridoxine, 50 mg a day.[4,43] Alternatively, isoniazid can be given as observed therapy twice a week (15 mg per kg up to 900 mg). Six months of therapy may suffice, but further studies are needed. For patients intolerant to isoniazid, taking rifampin, 600 mg a day for 3

to 12 months, is effective.[44] Rifabutin is being studied as an alternative to isoniazid for tuberculosis prophylaxis.

Persons with HIV infection and cutaneous anergy may be at increased risk of tuberculosis developing.[45,46] The value of routine anergy testing is unclear, however, because of the inconsistency of anergy testing over time and the lack of association of anergy with the risk of tuberculosis in some studies. Currently the USPHS-IDSA guidelines call for an individualized use of anergy testing.[4] The efficacy of isoniazid chemoprophylaxis in anergic HIV-infected patients has not been established.

Mycobacterium avium Complex

Without prophylaxis, a large proportion of HIV-infected patients may have disseminated *Mycobacterium avium* complex, usually in late-stage disease after the CD4 count has fallen below 50×10^6 per liter.[47] Disseminated *M avium* complex is associated with fever, weight loss, decreased quality of life, and increased mortality.[48,49] Treatment of the disease usually requires lifelong combination therapy.

The combined data from two identical double-blind studies comparing the use of rifabutin, 300 mg a day, with that of placebo in patients with AIDS and a CD4 count of less than 200×10^6 per liter showed that bacteremia developed in 48 of 566 (8%) patients assigned to receive rifabutin and 102 of 580 (18%) patients assigned to receive placebo during a mean follow-up of 205 days.[50] Persons assigned to receive rifabutin had a delayed onset of fatigue and fever, as well as a decreased incidence of hospitalization, a decline in the hemoglobin level, and a decline in the Karnofsky score. Fewer deaths occurred in patients taking rifabutin—33 of 566 (5.8%) compared with 47 of 580 (8.1%); the difference was not statistically significant, however. Recent long-term follow-up data suggest that the use of rifabutin prolongs survival.[51] Therapy was discontinued because of adverse events in 16% of patients receiving rifabutin and 8% of placebo recipients. Rash, gastrointestinal distress, and neutropenia were the most commonly noted.

Uveitis has occurred with the administration of rifabutin at higher doses, and it has been reported in several patients receiving rifabutin for prophylaxis at the recommended dose of 300 mg a day.[52] Most patients with rifabutin-associated uveitis were also receiving fluconazole, which is known to increase rifabutin concentrations.[53] Rifabutin induces hepatic microsomal enzymes, which can affect the metabolism of many drugs including oral contraceptives, warfarin sodium, phenytoin (Dilantin), methadone, zidovudine, and saquinavir mesylate. *Mycobacterium avium* complex organisms from patients taking rifabutin in whom bacteremia develops do not show notable resistance to rifabutin.

Clarithromycin has also been studied as a prophylactic agent for *M avium* complex infection. In a multicenter trial comparing the use of clarithromycin, 500 mg twice a day, with that of placebo, treated patients had a 68% decrease in the incidence of bacteremia ($P < .001$) and a 30% decrease in mortality ($P = .016$).[54] In this trial, however, 58% of the breakthrough organisms were resistant to clarithromycin, the most important drug in the treatment of disseminated *M avium* complex.

The initial results of two recently reported trials find both clarithromycin and azithromycin more effective than rifabutin for *M avium* prophylaxis.[55,56] Both these studies also found the combination of rifabutin with either clarithromycin or azithromycin to be more efficacious than monotherapy with any agent. In addition, the rates of macrolide resistance in breakthrough organisms was considerably lower than previously reported. Because the use of rifabutin is not recommended for patients taking protease inhibitors, macrolides may become the preferred agents for *M avium* prophylaxis.

The USPHS-IDSA guidelines recommend that prophylaxis with rifabutin, 300 mg a day, be considered in patients with CD4 counts of less than 75×10^6 per liter.[4] Clarithromycin, 500 mg twice a day, or azithromycin dihydrate, 1,200 mg weekly, are effective alternatives and are recommended for patients taking protease inhibitors. All patients should be assessed before prophylaxis is instituted to ensure they do not have active tuberculosis, and a blood culture should be done to rule out the presence of disseminated *M avium* complex.

Fungal Prophylaxis

The occurrence of fungal infections increases dramatically as CD4 counts decline. The most serious of these, cryptococcal meningitis, affects 8% to 15% of patients with AIDS, usually when the CD4 count is less than 50×10^6 per liter.[57] Mucocutaneous candidiasis occurs in more than 90% of patients, with *Candida* species esophagitis affecting more than 15% of patients.[57] Endemic mycoses, such as histoplasmosis and coccidioidomycosis, affect 15% to 25% of patients from endemic areas.[57,58] Although the incidence of cryptococcal disease is relatively low, the morbidity and mortality associated with cryptococcosis make it a possible target for prophylaxis.

Fluconazole was effective in preventing serious fungal infections in one controlled clinical trial (AIDS Clinical Trials Group study 981). In this trial, 428 patients with CD4 counts of less than 200×10^6 per liter were randomly assigned to receive fluconazole (200 mg a day) or clotrimazole troches (10 mg 5 times a day).[59] Invasive fungal infections occurred in 9 of 217 patients (4%) assigned to receive fluconazole, compared with 23 of 211 patients (11%) assigned to receive clotrimazole ($P = .02$). The proportion of patients with cryptococcosis was 1% in the fluconazole-treated group and 7% in the clotrimazole-treated group ($P = .004$). Similarly, *Candida* species esophagitis occurred in 1% and 8% of patients in the two groups, respectively ($P = .004$). The benefit was most pronounced among patients with CD4 counts of less than 50×10^6 per liter. There was no difference in mortality between the two groups. An earlier study of patients given fluconazole at a dose of 100 mg a day found a protective effect against cryptococcal disease compared with historical controls.[60]

The most important drawbacks to routine antifungal prophylaxis are cost, drug interactions, and the potential for promoting infection with fluconazole-resistant *Can-*

TABLE 1.—*Prevention of Opportunistic Infections—Antimicrobial Prophylaxis*

Pathogen	*Indications for Prophylaxis*	*Regimens*
Pneumocystis carinii pneumonia. . . .	Previous *P carinii* pneumonia; CD4 <200 × 10^6/liter; unexplained fevers >2 wk; oropharyngeal candidiasis	Preferred regimen: TMP-SMX, 1 double-strength (DS) tablet/day Alternatives: • TMP-SMX, 1 single-strength (SS) tablet/day or 1 DS 3×/wk • Dapsone, 100 mg/day • Dapsone, 50 mg/day, + pyrimethamine, 50 mg/wk, + leucovorin, 25 mg/wk • Dapsone, 200 mg/wk, + pyrimethamine, 75 mg/wk, + leucovorin, 25 mg/wk • Aerosolized pentamidine, 300 mg/mo
Toxoplasmosis	CD4 <100 × 10^6/liter and anti-*Toxoplasma* IgG antibody	Preferred regimen: TMP-SMX, 1 DS/day Alternatives: • TMP-SMX, 1 SS/day, or 1 DS 3×/wk • Dapsone, 50 mg/day, + pyrimethamine, 50 mg/wk, + leucovorin, 25 mg/wk
Mycobacterium tuberculosis	PPD positive (≥ 5 mm induration); previous positive PPD untreated; high-risk exposure	Preferred regimen: isoniazid, 300 mg/day, + pyridoxine, 50 mg/day for 12 mo Alternatives: • Isoniazid, 15 mg/kg (up to 900 mg) 2×/wk, + pyridoxine, 50 mg 2×/wk, directly observed therapy, for 12 mo • Rifampin, 600 mg/day for 3-12 mo
Mycobacterium avium complex	CD4 <75 × 10^6/liter	Rifabutin, 300 mg/day Clarithromycin, 500 mg 2×/day Azithromycin, 1,200 mg/wk
Serious fungal infections.	Consider in patients with CD4 <50 × 10^6/liter	Preferred regimen: fluconazole, 200 mg/day
Cytomegalovirus (CMV)	Consider in patients with CD4 <50 × 10^6/liter, anti-CMV IgG, and positive blood PCR	Preferred regimen: ganciclovir, 1,000 mg orally 3×/day
Bacterial infections	All patients	23-valent pneumococcal polysaccharide vaccine, 0.5 ml intramuscularly

IgG = immunoglobulin G, PCR = polymerase chain reaction, PPD = purified-protein derivative, TMP-SMX = trimethoprim-sulfamethoxazole

dida species. Such infection appears to be associated with a prolonged or early use of fluconazole,[61] and patients with fluconazole-resistant mycoses may require long-term therapy with intravenous amphotericin B. The cost to prevent a single case of invasive mycosis if all HIV-infected patients with CD4 counts of less than 200 × 10^6 per liter were given fluconazole, 200 mg a day, has been estimated to be $100,000.[59] Although fluconazole is generally well tolerated, about 15% of patients will have associated abdominal pain or nausea.[59]

Antifungal prophylaxis may be considered for patients at greatest risk for cryptococcal meningitis (CD4 count <50 × 10^6 per liter). Other considerations in prescribing antifungal prophylaxis include possible drug interactions, the complexity of medication regimens, and compliance. Long-term fluconazole therapy is indicated for patients with recurrent candidal esophagitis or with a history of treated cryptococcal meningitis. To date there is insufficient evidence to support the use of primary prophylaxis for histoplasmosis or coccidioidomycosis for patients from endemic areas. Studies are under way to determine the efficacy of intermittent high-dose fluconazole prophylaxis (such as 1,200 mg a week).

Cytomegalovirus Infection

As much as 90% of AIDS patients at autopsy have evidence of active CMV infection,[62] and sight- or life-threatening infections may develop in as much as 40% of patients as they become immunosuppressed and CD4 counts fall below 100 × 10^6 per liter.[63,64] Given the sight-threatening morbidity associated with CMV, the toxicity and expense of parenteral treatment, and the inability to maintain effective permanent remission in most patients, CMV disease is an appropriate target for prophylaxis.

Acyclovir is ineffective in preventing CMV disease in HIV-infected patients.[65] Preliminary analysis of a randomized trial of oral ganciclovir (1,000 mg 3 times a day) showed a 50% reduction in the incidence of CMV disease in the treated group.[66] Oral ganciclovir prophylaxis does not appear to affect ganciclovir susceptibility of the viral organisms that cause breakthrough disease.[67] A second trial of oral ganciclovir prophylaxis for CMV disease did not find a benefit.[68] The latter study did not include active monitoring for retinitis, however, and a large proportion of patients were crossed over to receive open-label oral ganciclovir.

Indications for oral ganciclovir prophylaxis remain to be determined. Targeting prophylaxis to patients with CD4 counts of less than 50 × 10^6 per liter and positive blood CMV polymerase chain reactions may be the most effective approach. To prevent infection, patients without serologic evidence of previous CMV infection should receive only CMV-negative blood products when transfusions are required.

Bacterial Infections

Infections with common bacterial pathogens occur with increased frequency in HIV-infected persons. These include *Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa,* and *Salmonella* species. Trimethoprim-sulfamethoxazole, used for the prophylaxis of *P carinii* pneumonia, has been shown to decrease the incidence of serious bacterial infections by 50% compared with aerosolized pentamidine.[12] The 23-valent polysaccharide vaccine is recommended by the USPHS-IDSA for all HIV-infected patients.[4] The efficacy of pneumococcal vaccine for patients with HIV and CD4 counts of greater than 200 × 10^6 per liter has recently been sug-

gested in a case-control study.[69] The vaccine should be given as early as possible in the course of illness to maximize the likelihood of an immune response. Vaccination against *H influenzae* type b is not routinely recommended as most strains of *Haemophilus* infecting adults are non–type b strains. Administering azithromycin and clarithromycin, given for *M avium* prophylaxis, also reduces the incidence of bacterial infections, particularly respiratory tract disease.[56,55]

Further Considerations Regarding Prophylaxis

Several therapies prevent or delay opportunistic infections in patients with HIV infection (Table 1). Clearly, prophylaxis against *P carinii* pneumonia is essential for patients with AIDS. Prophylaxis against toxoplasmosis and disseminated *M avium* complex also appears to be important in susceptible patients, and CMV disease and serious fungal infections are also preventable. The overall effect of patients taking several drugs for prophylaxis has not been established, however. Polypharmacy is often complicated by drug interactions and poor patient compliance. As noted previously, patients taking rifabutin and fluconazole may have a rise in serum rifabutin concentrations that may increase the rates of adverse drug effects. Administering rifabutin and clarithromycin decreases serum concentrations of zidovudine,[70,71] which may reduce the benefit of this antiretroviral agent. Thus, although there are many prophylactic agents available with proven efficacy, clinicians must tailor each patient's regimen and remain aware of new information regarding the overall efficacy of complex regimens. Future regimens, it is hoped, will combine broad efficacy against possible pathogens with acceptable toxicity, drug interactions, and cost.

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